

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**50-767**

**CORRESPONDENCE**



# Pharmacia & Upjohn

Office of:  
Nancy Busso, R.Ph.  
Regulatory Manager  
Regulatory Affairs

Telephone No. (616) 833-8554  
Facsimile No. (616) 833-8237

October 13, 1998

Division of Special Pathogens and Immunologic  
Drug Products (HFD-590)  
Center for Drug Evaluation Research  
Food and Drug Administration  
9201 Corporate Blvd.  
Rockville, MD 20850

RE: NDA 50-767  
CLEOCIN® Vaginal Ovule  
(clindamycin phosphate vaginal suppository)

ORIGINAL NDA SUBMISSION

Dear Sir or Madam:

Under the provisions of 21 CFR 314.50, we are submitting a New Drug Application, NDA 50-767, for CLEOCIN® Vaginal Ovules (clindamycin phosphate vaginal suppositories) indicated for the treatment of bacterial vaginosis. (Please note, the terms "ovule" and "suppository" are used synonymously throughout the document.)

By prior arrangement with the Agency from a teleconference held on 24 August 1998, the archival and review copies of Items 11 and 12 have been included as hard copy.

This application consists of 117 volumes as described in the following outline:

<u>Item</u>	<u>Overall Volume Number</u>
Cover letter	1.1
Form FDA 356h	1.1
Item 13 Patent Information	1.1
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Item 16 Debarment Certification	1.1
Item 17 Certification of Field Copy	1.1
Item 18 User Fee Cover Sheet	1.1
Note to Reviewers	1.1
Item 1 Application Index	1.1
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NDA 50-767  
Cleocin Vaginal Ovule  
Original NDA Submission  
Page 2

Item 3 Summary	1.3
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Item 5 Nonclinical Pharmacology and Toxicology	1.6 - 1.22
Item 6 Human Pharmacokinetics Bioavailability	1.23 - 1.33
Item 7 Microbiology	1.34 - 1.37
Item 8 Clinical Data Section	1.38 - 1.74
Item 10 Statistical Section	1.75 - 1.111
Item 11 Case Report Tabulations	1.112 - 1.116
Item 12 Case Report Forms	1.117

In conjunction with this New Drug Application, we have submitted a User Fee in the amount of  under User Fee Number 3541.

If you have questions related to this submission, please contact me at (616) 833-8554 or address correspondence to mailstop 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

*Nancy J. Busso*

Nancy J. Busso  
Regulatory Manager  
Regulatory Affairs

cc: Christina Chi

NJB:law

Form FDA 356h

ITEM 13 Patent  
Information

ITEM 14 Patent  
Certificate

ITEM 16 Debarment  
Certification

ITEM 17 Certification of  
Field Copy



# Pharmacia & Upjohn

Office of:  
P.K. Narang, Ph.D., F.C.P.  
Director, New Drugs  
Regulatory Affairs

Telephone No. (616) 833-9896  
Facsimile No. (616) 833-8237

January 21, 1999

Mark Goldberger, MD  
Division of Special Pathogens and Immunologic  
Drug Products (HFD-590)  
Center for Drug Evaluation Research  
Food and Drug Administration  
9201 Corporate Blvd.  
Rockville, MD 20850

RE: NDA 50-767  
CLEOCIN® Vaginal Ovule  
(clindamycin phosphate vaginal  
suppository)

Dear Dr. Goldberger:

As requested by Dr. Leji Shen, statistical reviewer for CLEOCIN Vaginal Ovules, the SAS datasets for this application are enclosed. This information includes the datasets and appropriate documentation for Protocols M/1114/0001, M/1114/0002 and M/1100/0283.

In addition to the electronic version, hard copy has been provided for the directory of the domain datasets, a list and the corresponding definitions of the derived variables by domain dataset and data definition tables for each of the three protocols including an annotated case report form for each study.

If you have any questions regarding the contents of this submission, please contact P.K. Narang (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

*Daniel G. Mannix for*  
P.K. Narang, Ph.D., F.C.P.  
Regulatory Affairs

PKN:crd/Attachments

Desk Copy: Dr. Leji Shen

Pharmacia & Upjohn  
7000 Portage Road  
Kalamazoo, MI 49001-0199  
USA

Telephone (616) 833-4000

Pre NDA telecon 2/26/1998

= Pharmacia Upjohn Telecon ~~32~~ - 616-833-9832 July Conf  
2433 Conf. Rm

Hudry, Tom Snyder

Dick Thomas

Proposal: { Items 11 & 12 case report  
hard copy + electronic

BL: endpoint → Guidance: electr<sup>version</sup> will be the archival

NB: provide disks (SAS datasets)

BL: { case report form  
section 12: the patient's (report form) on diskettes?  
CD Rom. Will be helpful if sent in

{ Case report tabulation < paper format (hardcopy)  
electronic version in PDF.  
not just the CR forms

Section 11: Can send both paper + PDF.

3 Studies: (2) Oule > Vag. cream.

(1) — > metronidazole.

{ Summary table of effic. & safety in Word format  
Send message re: <sup>C.F.</sup> issues on many from studies  
in electronic form. { labeling — already.

Questions on BV → in adv. com.

How studies are being conducted: CDER Intramnet Website  
~~Overhead containing questions re BV~~

Pre NDA mtg: Send a sample of the formats to Dr. W  
not necessary <sup>if this meeting is considered</sup> as an orientation project

Question: <sup>As play meeting of Cleocin Ovule</sup> patent information → Can this get exclusivity?  
NDA 50-767 Cleocin Ovule. NDA 50-767  
NO 5

Chem: fileable. (Most likely no nomenclature problem)  
Bio Pharm: fileable. no applicator? How do you apply?  
Ask for sample?  
How long does it take to melt?

Clinical fileable 3 studies → 1, placebo  
Dose range to see which <sup>looks better</sup>  
regimen to use. 3 days  
of 2 double dummy: < European: Ovule vs oral  
(nifedipine) 7 day  
vs 3d. Ovule vs. 7 day  
Cleocin Cream approved for B.I.  
looks better

Will give Christine a list to be forwarded to DS,  
~~DSI~~ ~~Micro~~ Micro: OK.

Ph.Tox → fileable

Please Resubmit Print is bad  
We can't read  
electronic version? Chem. Micro?  
BioStat

9 mo NDA day.



# Pharmacia & Upjohn

Office of:  
Carl M. De Juliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

Telephone No. (616) 833-9164  
Facsimile No. (616) 833-8237

March 8, 1999

Dr. Joseph Winfield  
Division of Special Pathogens and Immunologic  
Drug Products (HFD-590)  
Center for Drug Evaluation Research  
Food and Drug Administration  
9201 Corporate Blvd.  
Rockville, MD 20850

*Dr. Winfield  
instructed Christina Cline  
not to record this  
submission. It is on duplicate  
submissions already included in  
the NDA.*

RE: NDA 50-767  
CLEOCIN® Vaginal Ovule  
(clindamycin phosphate vaginal  
suppository)

## Desk Copy

Dear Dr. Winfield:

As requested on 3/2/99, we are providing the following electronic files for your use:

### 1. Disk #1

1. ISS in WORD (file = ISS.doc)
2. ISE in WORD (file = ISE.doc)
3. Main body of Study Report TR 9150-98-002 for Protocol M/1114/0001 in WORD

4. Main body of Study Report TR 9150-97-003 for Protocol M/1100/0283 in WORDPERFECT 5.2. The addendum is also included.

### 2. Disk #2

1. Main body of Study Report TR 9150-97-001 for Protocol M/1114/0002 in WORDPERFECT 5.2. The erratum and addendum is also included.

All disks have been scanned with Dr. Solomon Virus Scan software (7.89) to verify they are free of viruses.

If you have any questions regarding the contents of this submission, please contact  
Carl M. DeJuliis (616) 833-9164. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



Carl M. DeJuliis, MS, RPh  
Regulatory Affairs

CMD:lmf

cc: Dr. Christina Chi (FDA)

Attachments



**Pharmacia & Upjohn**

Office of:  
Carl M. De Juliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

Telephone No. (616) 833-9164  
Facsimile No. (616) 833-8237

March 22, 1999

Division of Special Pathogens and Immunologic  
Drug Products (HFD-590)  
Center for Drug Evaluation Research  
Food and Drug Administration  
9201 Corporate Blvd.  
Rockville, MD 20850

RE: NDA 50-767  
CLEOCIN® Vaginal Ovule  
(clindamycin phosphate vaginal  
suppository)

Amendment  
MANUFACTURING SITE FOR DRUG  
SUBSTANCE

Dear Sir/Madam:

In our application for Cleocin Vaginal Ovule, NDA 50-767, dated October 13, 1998, the 356h identifies Pharmacia & Upjohn Company, 7000 Portage Road, Kalamazoo, Michigan, 49001 and Pharmacia & Upjohn Arecibo, Hwy. No. 2, Km 60.0, Arecibo, Puerto Rico, 00612 [redacted] (Clindamycin Phosphate). Item 3.4.2.b of this submission only identified Pharmacia and Upjohn Caribe, Inc., Arecibo, Puerto Rico, 00612 [redacted].

We are submitting this letter with a new 356h to eliminate the inconsistency between the original 356h and the original application. For Cleocin Vaginal Ovule, NDA 50-767, the manufacturing site for the drug substance (Clindamycin Phosphate) is Pharmacia and Upjohn Caribe, Inc., Arecibo, Puerto Rico, 00612. [redacted]

NDA 50-767  
Page 2

If you have any questions regarding the contents of this submission, please contact  
Carl M. DeJuliis (616) 833-9164. Please send correspondence addressed to Unit 0635-  
298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

*Carl M. DeJuliis*

Carl M. DeJuliis, MS, RPh  
Regulatory Affairs

CMD:crdt

Attachments

APPEAR THIS WAY  
ON ORIGINAL



Pharmacia & Upjohn

ORIGINAL

Office of:  
Donald R. Gieseke, Pharm.D.  
Associate Director  
Regulatory Affairs

Telephone No. (616) 833-8527  
Facsimile No. (616) 833-8237

March 24, 1997

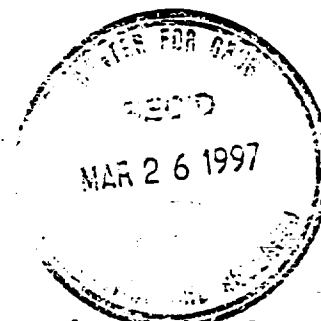
Division of Anti-Infective Drug Products HFD-520  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
9201 Corporate Boulevard  
Rockville, MD 20850

*OK - 6/6/97 - should go  
to a BioPharm  
reviewer @*

Re: [REDACTED] CLEOCIN® Vaginal Ovule  
(clindamycin phosphate)

Protocol Amendment  
Change in Site

Information Amendment  
Clinical Study Report



Dear Sir/Madam:

We are amending the above referenced IND to provide information as described in the following outline.

**Item 6 - Protocols**

**Change in Site**

Protocol M/1114/0001: Efficacy of Clindamycin Vaginal Ovule (3-day Treatment) vs Clindamycin Vaginal Cream (7-day Treatment) in Bacterial Vaginosis. (Protocol previously submitted on 10/28/94) [REDACTED]

1. Investigator:

[REDACTED]

**Clinical Study Report**

TR 7215-96-047 [REDACTED] Bioavailability of clindamycin in healthy females following administration of either the clindamycin phosphate vaginal ovule or vaginal cream (Protocol M/1114/0003 submitted 12/6/95) [REDACTED]  
pages 4-266

  
Page 2

If you have any questions regarding this submission, please contact Donald R. Gieseke at (616) 833-8527. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



Donald R. Gieseke, Pharm.D.  
Associate Director  
Regulatory Affairs

DRG:SEH  
Attachments

APPROPRIATE  
ORIGINAL

**Pharmacia & Upjohn**

Office of:  
Carl M. De Juliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

Telephone No. (616) 833-9164  
Facsimile No. (616) 833-8237

May 12, 1999

Division of Special Pathogens and Immunologic  
Drug Products (HFD-590)  
Center for Drug Evaluation Research  
Food and Drug Administration  
9201 Corporate Blvd.  
Rockville, MD 20850

RE: NDA 50-767  
CLEOCIN® Vaginal Ovule  
(clindamycin phosphate vaginal  
suppository)

**Safety Update**

Dear Sir/Madam:

Pharmacia and Upjohn would like to submit a Safety Update Report for Cleocin Vaginal Ovule. The NDA for Cleocin Vaginal Ovule was submitted on October 13, 1998. Since this submission, no new safety information that affects the contraindications, warning, precautions, and adverse reactions have been noted. Presently for this product, there are no current marketing or on-going studies.

If you have any questions regarding the contents of this submission, please contact Carl M. DeJuliis (616) 833-9164. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA &amp; UPJOHN COMPANY

Carl M. DeJuliis, MS, RPh  
Regulatory Affairs

CMD:SEH

[Redacted Box]

Food and Drug Administration  
Center for Drugs and Biologic  
Drug Master File Staff  
Central Document Room (Room 2-14)  
12420 Parklawn Dr.  
Rockville, MD 20852

Drug Master file: [Redacted]  
Date of Submission: 21 May 1999  
Title of Submission: Type III ; Plastic container & applicator device as  
[Redacted]  
Holder/Submitter [Redacted]

Attn: DMF Staff

We hereby authorize the Food and Drug Administration to refer to and incorporate by reference our Drug Master File Number [Redacted] for the Vaginal Suppository Applicator file when requested by:

Pharmacia & Upjohn  
7000 Portage Road  
Kalamazoo, MI 49001

We certify that the facilities, methods, and controls used in the production of the Vaginal Suppository Applicator conform with Good Manufacturing Practices as specified in 21 CFR 820.

It is assumed the incorporation by reference does not constitute public disclosure and that confidentiality of the referenced material will be preserved.

Sincerely,       

/S/

[Redacted Box]



Pharmacia & Upjohn

7000 Portage Road  
Kalamazoo, MI 49001-0199  
Telephone: (616) 833-4000

Office of:  
Carl M. De Juliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

Telephone No. (616) 833-9164  
Facsimile No. (616) 833-8237

June 3, 1999

Philip Colangelo, PhD  
Food and Drug Administration  
Division of Pharmaceutical Evaluation III (HFD-880)  
Room 330  
9201 Corporate Blvd  
Rockville, MD 20850

RE: NDA 50-767  
CLEOCIN® Vaginal Ovule  
(clindamycin phosphate vaginal  
suppository)

Desk Copy: Review Aids

Dear Dr. Colangelo:

As requested on June 1 and 2, 1999, please find enclosed the following review aids:

1. A binder containing a desk copy of TR 7215-91-012
2. A binder containing a desk copy of TR 7227-95-004
3. A diskette containing file 721596047.wp5 (the body of TR 7215-96-047 in WordPerfect 5.2). This diskette has been scanned with VirusScan NT Version 4.02 and is free of viruses.

If you have any questions regarding the contents of this submission, please contact  
Carl M. DeJuliis (616) 833-9164. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Carl M. DeJuliis, MS, RPh  
Regulatory Affairs

CMD:lmf

cc: Dr. Christina Chi (FDA)  
Attachments

*Phil Received all on 6/4/99.  
Verified by Doc Rm*

**Pharmacia & Upjohn**

7000 Portage Road  
Kalamazoo, MI 49001-0189  
Telephone: (616) 833-4000

Office of:  
Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

Telephone No. (616) 833-9164  
Facsimile No. (616) 833-8237

July 8, 1999

Division of Special Pathogens and Immunologic  
Drug Products (HFD-590)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
9201 Corporate Boulevard  
Rockville, MD 20850

RE: NDA 50-767  
CLEOCIN® Vaginal Ovule  
(clindamycin phosphate vaginal  
suppository)

General Correspondence  
Responses to Chemistry Questions  
Dated June 5 and 21, 1999

Dear Sir/Madam:

Please find appended our responses to the questions that Dr. Matecka raised concerning Clindamycin Phosphate Vaginal Suppository (NDA #50-767) in her memos dated June 5, 1999 and June 21, 1999.

Questions regarding the labeling for the use of the applicator, the labeling of the immediate container, and the functionality testing of the applicator will be provided in the near future. We are currently working on the responses to these questions and hope to provide those to you shortly.

If you have any questions regarding this submission, please contact Carl DeJuliis at (616) 833-9164. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

*Carl M. DeJuliis*

Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

CMD:lmf  
Attachments

*sent July 13, 99*



**Pharmacia & Upjohn**7000 Portage Road  
Kalamazoo, MI 49001-0189  
Telephone: (616) 833-4000Office of:  
Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory AffairsTelephone No. (616) 833-9164  
Facsimile No. (616) 833-8237

July 13, 1999

Division of Special Pathogens and Immunologic  
Drug Products (HFD-590)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
9201 Corporate Boulevard  
Rockville, MD 20850RE: NDA 50-767  
CLEOCIN® Vaginal Ovule  
(clindamycin phosphate vaginal  
suppository)General Correspondence  
Responses to Chemistry Questions  
Dated June 5 and 21, 1999

Dear Sir/Madam:

Please find appended our responses to the outstanding questions that Dr. Matecka raised concerning Clindamycin Phosphate Vaginal Suppository (NDA #50-767) in her memos dated June 5, 1999 and June 21, 1999. It is our belief, that this completes our responses to the chemistry questions. If this is not so, please let us know.

If you have any questions regarding this submission, please contact Carl DeJuliis at (616) 833-9164. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA &amp; UPJOHN COMPANY

Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory AffairsCMD:mlw  
Attachments

Christina chi



Pharmacia & Upjohn

7000 Portage Road  
Kalamazoo, MI 49001-0199  
Telephone: (616) 833-4000

Office of:  
Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

Telephone No. (616) 833-9164  
Facsimile No. (616) 833-8237

July 20, 1999

Division of Special Pathogens and Immunologic  
Drug Products (HFD-590)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
9201 Corporate Boulevard  
Rockville, MD 20850

RE: NDA 50-767  
CLEOCIN® Vaginal Ovule  
(clindamycin phosphate vaginal  
suppository)

General Correspondence  
Responses to July 19, 1999 Request

Dear Sir/Madam:

Per a July 19, 1999 telephone conversation with Dr. Christina Chi, attached please find the requested information regarding the interaction between the Cleocin Vaginal Ovule and latex or rubber vaginal products (ie: condoms diaphragms).

The attached Interoffice Memo describes the study conducted to assess this interaction. Brief results are summarized.

If you have any questions regarding this submission, please contact Carl DeJuliis at (616) 833-9164. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

A handwritten signature in cursive script that reads "Carl M. DeJuliis".

Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

CMD:SEH  
Attachments



**Pharmacia & Upjohn**

7000 Portage Road  
Kalamazoo, MI 49001-0199  
Telephone: (616) 833-4000

Office of:  
Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

Telephone No. (616) 833-9164  
Facsimile No. (616) 833-8237

July 21, 1999

Division of Special Pathogens and Immunologic  
Drug Products (HFD-590)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
9201 Corporate Boulevard  
Rockville, MD 20850

RE: NDA 50-767  
CLEOCIN® Vaginal Ovule  
(clindamycin phosphate vaginal  
suppository)

General Correspondence  
DMF Authorization for the Vaginal  
Suppository Applicator.

Dear Sir/Madam:

In our original application dated October 13, 1998, we referenced [ ] as the file that contained information regarding the supplied vaginal suppository applicator. For this applicator, [ ] is not the appropriate file. The information regarding the applicator is contained in [ ]. Attached is the authorization for [ ].

If you have any questions regarding this submission, please contact Carl DeJuliis at (616) 833-9164. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

CMD:mlw  
Attachments

cc: Dr. Christina Chi

**Pharmacia & Upjohn**

7000 Portage Road  
Kalamazoo, MI 49001-0189  
Telephone: (616) 833-4000

Office of:  
Carl M. DeJulius, MS, RPh  
Regulatory Manager  
Regulatory Affairs

Telephone No. (616) 833-9164  
Facsimile No. (616) 833-8237

July 26, 1999

Division of Special Pathogens and Immunologic  
Drug Products (HFD-590)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
9201 Corporate Boulevard  
Rockville, MD 20850

RE: NDA 50-767  
CLEOCIN® Vaginal Ovule  
(clindamycin phosphate  
vaginal suppository)

General Correspondence  
Request for Pediatric Waiver

Dear Sir/Madam:

Pursuant to 314.55(c) (2), Pharmacia and Upjohn wishes to request a full waiver of the pediatric study requirement for the Cleocin Vaginal Ovule NDA.

Bacterial vaginosis (BV) is a rare event in premenarchal females. Bacterial vaginosis is not listed as a distinct entity in the National Drug and Therapeutic Index of IMS database, however, bacterial vaginitis is. The total diagnosis of bacterial vaginitis from this office base/retail sector database for patients 16 and under was  for the 5/98 to 5/99 period. We believe the majority of these cases represent postmenarchal females.

Given the prevalence of the disease and route of administration (vaginally) of the Cleocin Vaginal Ovule, it is unlikely that a substantial number of premenarchal females would use this medication. For postmenarchal females, we believe that adult clinical trial data can be extrapolated to demonstrate safety and effectiveness in this group.

NDA 50-767

Page 2

Based on the above information, we request a waiver of the pediatric study requirement.

If you have any questions regarding this submission, please contact Carl DeJuliis at (616) 833-9164. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

CMD:lmf

APPEARS THIS WAY  
ON ORIGINAL

**Pharmacia & Upjohn**7000 Portage Road  
Kalamazoo, MI 49001-0199  
Telephone: (616) 833-4000Office of:  
Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory AffairsTelephone No. (616) 833-9164  
Facsimile No. (616) 833-8237

July 26, 1999

Division of Special Pathogens and Immunologic  
Drug Products (HFD-590)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
9201 Corporate Boulevard  
Rockville, MD 20850RE: NDA 50-767  
CLEOCIN® Vaginal Ovule  
(clindamycin phosphate vaginal  
suppository)General Correspondence  
Geriatric Labeling Change

Dear Sir/Madam:

Pursuant to 21 CFR 201.57(f)(10)(ii)(A), Pharmacia and Upjohn wishes to revise the geriatric use section of our proposed label for Cleocin Vaginal Ovule NDA. We will replace the current wording with the following wording:

Clinical studies of Cleocin Vaginal Ovule did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Modification (deletion of last sentence) of the standard text was required because it is not applicable for the present dosage form and therapy.

If you have any questions regarding this submission, please contact Carl DeJuliis at (616) 833-9164. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA &amp; UPJOHN COMPANY

Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs  
CMD:lmf

**Pharmacia & Upjohn**

7000 Portage Road  
Kalamazoo, MI 49001-0199  
Telephone: (616) 833-4000

Office of:  
Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

Telephone No. (616) 833-9164  
Facsimile No. (616) 833-8237

July 27, 1999

Division of Special Pathogens and Immunologic  
Drug Products (HFD-590)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
9201 Corporate Boulevard  
Rockville, MD 20850

RE: NDA 50-767  
CLEOCIN® Vaginal Ovule  
(clindamycin phosphate vaginal  
suppository)

General Correspondence  
Carton Label Mock-up

Dear Sir/Madam:

As requested, please find enclosed two color mock-ups of the proposed Cleocin Vaginal Ovule carton labeling. On the front carton panel, the net quantity of content will be changed from 3 - 100 mg Suppositories to 3 Suppositories. On the back carton panel, the words "US Patent Number No. xxxxxx" will be deleted.

If you have any questions regarding this submission, please contact Carl DeJuliis at (616) 833-9164. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

A handwritten signature in cursive script that reads "Carl M. DeJuliis".

Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

CMD:lmf  
Enclosures



**Pharmacia & Upjohn**

7000 Portage Road  
Kalamazoo, MI 49001-0199  
Telephone: (616) 833-4000

Office of:  
Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

Telephone No. (616) 833-9164  
Facsimile No. (616) 833-8237

August 5, 1999

Division of Special Pathogens and Immunologic  
Drug Products (HFD-590)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
9201 Corporate Boulevard  
Rockville, MD 20850

RE: NDA 50-767  
CLEOCIN® Vaginal Ovule  
(clindamycin phosphate  
vaginal suppository)

General Correspondence  
**LABELING**

Dear Sir/Madam:

Pharmacia and Upjohn (PNU) would like to submit the following items to NDA 50-767:

- Attachment 1: An August 2, 1999 E-mail from Carl M. DeJuliis, PNU, to Dr. Brad Leissa, FDA. This correspondence contains information regarding the number of subjects enrolled and the reporting of abnormal labor during PNU's pregnancy studies with the Cleocin Vaginal Cream.
- Attachment 2: An August 3, 1999 E-mail from Carl M. DeJuliis, PNU, to Dr. Brad Leissa, FDA. This correspondence contains information on the digital insertion of Cleocin Vaginal Ovules during pivotal clinical trials.
- Attachment 3: Proposed carton and foil labeling (actual size) for Cleocin Vaginal Ovules.

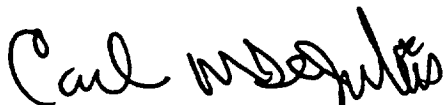
Attachments 1 and 2 were submitted previously to Dr. Brad Leissa, FDA, Medical Team Leader, electronically during label negotiations.



If you have any questions regarding this submission, please contact Carl DeJuliis at (616) 833-9164. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

CMD:kmv  
Enclosures

RECEIVED IS NOT  
OF ORIGINAL



Pharmacia & Upjohn

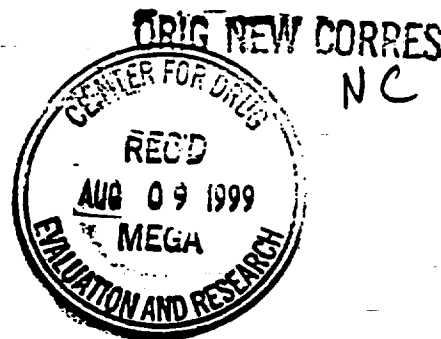
7000 Portage Road  
Kalamazoo, MI 49001-0199  
Telephone: (616) 833-4000

Office of:  
Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

Telephone No. (616) 833-9164  
Facsimile No. (616) 833-8237

August 6, 1999

Division of Special Pathogens and Immunologic  
Drug Products (HFD-590)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
9201 Corporate Boulevard  
Rockville, MD 20850



RE: NDA 50-767  
CLEOCIN® Vaginal Ovule  
(clindamycin phosphate vaginal  
suppository)

General Correspondence  
Responses to Chemistry Questions  
Dated July 20, 1999

Dear Sir/Madam:

Pursuant to the July 28, 1999 and August 6, 1999 teleconferences between the FDA and Pharmacia and Upjohn, please find appended our responses to the outstanding questions that Dr. Matecka raised concerning Clindamycin Phosphate Vaginal Suppository (NDA #50-767) in her fax dated July 20, 1999. It is our belief, that this completes our responses to the chemistry questions. If this is not so, please let us know.

If you have any questions regarding this submission, please contact Carl DeJuliis at (616) 833-9164. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

CMD:crdt  
Attachments

ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

Date: August 11, 1999

To: Pharmacia & Upjohn  
Att: Carl M. DeJuliis

From: Dorota Matecka, Ph.D., Chemistry Reviewer  
Division of Special Pathogens and Immunologic Drug Products, HFD-590

Through: Norman R. Schmuff, Ph.D., Chemistry Team Leader *NR 8/11/99*  
Division of Special Pathogens and Immunologic Drug Products, HFD-590

Re: NDA 50-767 (clindamycin phosphate vaginal suppositories)

Please address the following comment regarding the labeling for NDA 50-767:

1. Please increase the prominence of the established name in all parts of labeling, including the carton, physician package insert and suppository shell. In order to expedite our action on this application, consider proposing three alternate presentations, in which the established name has a prominence commensurate with the prominence of the proprietary name.

APPEARS THIS WAY  
ON ORIGINAL



Pharmacia & Upjohn

7000 Portage Road  
Kalamazoo, MI 49001-0199  
Telephone: (616) 833-4000

Office of:  
Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

Telephone No. (616) 833-9164  
Facsimile No. (616) 833-8237

August 12, 1999

Division of Special Pathogens and Immunologic  
Drug Products (HFD-590)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
9201 Corporate Boulevard  
Rockville, MD 20850

RE: NDA 50-767  
CLEOCIN® Vaginal Ovules  
(clindamycin phosphate vaginal  
suppositories)

General Correspondence  
Labeling

Dear Sir/Madam:

In a fax dated August 11, 1999, Dr. Matecka, Chemistry Reviewer, requested that the prominence of the established name on the carton, physician package insert and the foil (immediate container) be increased. In response her fax, please find enclosed labeling in which the size of the established name has been increased from the recommended 50% to at least 60 % of the proprietary name for all pieces.

If you have any questions regarding this submission, please contact Carl DeJuliis at (616) 833-9164. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Carl M. DeJuliis, MS, RPh  
Regulatory Manager  
Regulatory Affairs

CMD:crdt  
Attachments



DEPARTMENT OF HEALTH & HUMAN SERVICES

HFD 590

Food and Drug Administration  
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

NOV 17 1999

Beth E. Freeman  
Associate Director  
Global Promotion & Labeling  
Pharmacia & Upjohn  
7000 Portage Rd.  
Kalamazoo, MI 49001

RE: NDA #50-767  
Cleocin Vaginal Ovules (clindamycin phosphate vaginal suppositories)  
MACMIS ID #8388

Dear Ms. Freeman:

Reference is made to Pharmacia & Upjohn's (P&U) October 15, 1999, letter requesting comments on proposed promotional launch materials for Cleocin Vaginal Ovules. This submission consisted of the following promotional pieces:

- Sales Aid UX00762.00
- Physician Announcement Letter UD00764.00
- Patient/User Brochure UX00808.00

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the submission and offers the following comments. Our comments regarding a specific claim or presentation should be applied to all similar claims or presentations throughout all current and future promotional materials for Cleocin Vaginal Ovules.

**Sales Aid**

**Indication**

We note that the information regarding Cleocin Vaginal Ovules' indication is not presented with adequate prominence and readability. The indication is presented

as a small footnote at the bottom of page 2 of the sales aid that makes it difficult to see or read, and minimizes the importance of the information conveyed. This is important information regarding the appropriate use of the product and should be prominently presented in the body of the sales aid. Therefore, we recommend that you revise the sales aid to increase the prominence and readability of the indication information currently presented as a footnote.

### **Risk Information**

The proposed sales aid would be lacking in fair balance or otherwise misleading because certain risk information is not presented in a manner that is reasonable comparable with the presentation of promotional messages for the drug. Promotional materials must present information relating to contraindications, warnings, precautions, and side effects with a prominence and readability reasonable comparable with the presentation of promotional messages for the drug. Although you present the adverse events profile for Cleocin Vaginal Ovules with a prominence reasonably comparable to promotional claims for the drug, the information regarding the contraindications, warnings, and precautions associated with the use of this product is presented with less prominence, diminishing the importance of the information conveyed. Specifically, the information regarding Cleocin Vaginal Ovules favorable safety profile, e.g., low discontinuation rates and low incidence of local adverse events, is presented in large, bold print in bullet format. Conversely, information regarding the product's contraindications and warnings is presented in small type in paragraph format under the larger favorable safety profile presentation. Additionally, the precaution information regarding the use of this product to treat pregnant women is presented in even smaller type at the bottom of the last page of the sales aid. Therefore, we recommend that you revise the sales aid to present all of the fair balance information with a prominence reasonable comparable to the presentation of promotional messages/claims for Cleocin Vaginal Ovules.

We also recommend that you include the following information to complete the presentation of Cleocin Vaginal Ovules' safety profile:

- Patients should not engage in vaginal intercourse or use other vaginal products (e.g., tampons, or douches) during treatment with this product; and
- Latex or rubber products such as condoms or vaginal contraceptive diaphragms should not be used within 72 hours following treatment with Cleocin Vaginal Ovules because the base of the medication may weaken these latex products.

### **Physician Announcement Letter**

We refer you to the sales aid section for our comments regarding similar claims/presentations in the physician announcement letter. We have no further comments at this time.

### **Patient/User Brochure**

**"Bacterial vaginosis (BV) is the most common type of vaginal infection."**

To more accurately describe the condition, the prevalence, and the patient population in which this condition occurs, we recommend that you revise the above statement to, for example, "Bacterial vaginosis (BV) is the most common cause of vaginitis in women of childbearing age."

**"BV has been linked to other health problems. BV may also make you more likely to get other infections."**

The above statements are very broad and fail to provide a context that explains the relationship between BV and "other health problems" or "infections." Therefore, we recommend that you revise the above statements to explain this relationship.

**"Cleocin Vaginal Ovules are a new, prescription-only, 3-day treatment option for nonpregnant women with BV."**

The patient/user brochure would be misleading because the statement regarding the indication is incomplete. Specifically, the brochure fails to include the "Note" information. The "Note" information defines the basis for the diagnosis of BV and explains the need to rule out other organisms that cause vaginal infections. The "Note" is an integral part of the indication for the appropriate use of Cleocin Vaginal Ovules and must be expressed as part of the indication. Therefore, we recommend that all presentations of Cleocin Vaginal Ovules' indication prominently include the "Note" information in the body of the presentation.

**"The most common side effects are vaginitis and vaginal yeast infection."**

To ensure that consumers understand the terms "vaginitis" and "vaginal yeast infection," we recommend that you provide context that explains these terms in consumer friendly language. The contextual disclaimer should also explain the signs or symptoms associated with the referenced conditions, e.g., vaginal pain, etc.

**“However, as with other medications, side effects may occur.”**

The above statement would be misleading because it diminishes the message about the specific side effects associated with using Cleocin Vaginal Ovules. Therefore, we recommend that you delete the above phrase “as with other medications.”

### **Consumer Friendly Language**

We recommend that you simplify the language in the brochure so consumers can easily understand the meaning of the messages conveyed.

For example, we offer the following suggestions (suggestions are not comprehensive of the entire brochure):

<b>Current Word</b>	<b>Suggested Changes</b>
Vaginitis	Inflammation of the vagina
Rectum	Anus
Medications	Medicines
Consecutive	In a row
Persistent	Continuing
Vaginal intercourse	Vaginal intercourse (sex)

We recommend that you review the remainder of the brochure with the goal of simplifying its language.

### **Additional Recommendations:**

- Include the following section after the instructions for use:

#### **Can I use tampons to prevent Cleocin from leaking out?**

Do not use tampons while you are using Cleocin Vaginal Ovules. Tampons may remove some of the medicine from the vagina. You may use deodorant-free sanitary napkins or pads instead.

- Explain or describe, in consumer friendly language, the following medical conditions: regional enteritis, ulcerative colitis, and “antibiotic-associated” colitis.
- Include the information that patients should not rely on condoms and diaphragms to prevent pregnancy or sexually transmitted diseases while using Cleocin Vaginal Ovules.



- Add a nursing section after the pregnancy section, as follows:

**Can I use Cleocin Vaginal Ovules if I am nursing a baby?**

It is not known if Cleocin, administered vaginally, is passed to the nursing baby through the milk. Therefore, if you are nursing a baby, talk with your healthcare provider to decide if you should stop nursing or stop using Cleocin Vaginal Ovules.

If you have any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857.

DDMAC reminds you that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID # 8388 in addition to the NDA number.

Sincerely,

/s/

Jd Ann Spearmon, Pharm.D., M.P.A.  
Regulatory Review Officer  
Division of Drug Marketing,  
Advertising, and Communications